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OF THE
RHEUMATIC DISEASES

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ANNALS

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RHEUMATIC DISEASES

THE OFFICIAL JOURNAL OF

THE EMPIRE RHEUMATISM COUNCIL

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ANNALS
OF THE
RHEUMATIC DISEASES

AN ANALYSIS OF 388 CASES OF RHEUMATOID ARTHRITIS

By J. G. SCLATER

Rheumatoid arthritis is described as a polyarticular disease which is characterised by pain and swelling of the small and medium-sized joints of the body. The onset is usually insidious, but it may be acute, and muscular wasting not only around the affected joints but also throughout the body is a striking feature. The incidence is stated to be greatest in the age period 20 to 40, and females are more frequently affected than males.

It is a common experience, however, to find that this description by no means covers a great many of the cases of rheumatoid arthritis. For example, a man aged 65 to 70 may present an arthritis affecting wrists and metacarpal-phalangeal joints associated with muscular wasting. If such a clinical picture had been presented by a woman of 35 there would be no hesitation in making a diagnosis of rheumatoid arthritis, but can rheumatoid arthritis occur in a man of 70? Or again, a woman shortly after the menopause may develop pain, swelling and limitation of movement, with muscular wasting, in both knees, and a diagnosis of menopausal arthritis may be suggested. A year later, however, the wrists and fingers may show the characteristic changes of rheumatoid arthritis, and the original diagnosis may have to be changed. Other variations such as the disease remaining monoarticular for some months before other joints become affected, or where stiffness in the region of the joints is more striking than actual pain and swelling, make the diagnosis of rheumatoid arthritis in some cases uncertain and difficult.

Accordingly, in any analysis of cases of arthritis of the rheumatoid type it is essential that the criteria on which the diagnosis is made are clearly stated.

In this series a case was considered to be an arthritis of the rheumatoid type if it showed the following features:

1 The presence of persistent swelling of the peri-articular tissues in the region of more than one joint.

2. The involvement, either primarily or subsequently, of the wrist, metacarpal-phalangeal joints, or interphalangeal joints.

3. The presence of muscular wasting.

4. Radiological evidence, where available, compatible with a diagnosis of rheumatoid arthritis.

5. The absence of evidence that the arthritis was specific (*e.g.*, tuberculous, gonococcal) in origin.

On these grounds 388 cases which had been admitted to hospital during the period 1935-40 were chosen. The records were obtained from the following sources:

Royal Infirmary, Edinburgh	169 cases
Municipal Hospitals, Edinburgh	119 „
Royal Infirmary, Aberdeen	100 „
Total	388

154 cases were under the care of Professor Davidson (35 from his wards in the Royal Infirmary, and 119 cases from the medical unit of the Municipal Hospitals, Edinburgh). They were examined personally by the author. The 100 cases from the Royal Infirmary, Aberdeen, were investigated by Dr. J. J. R. Duthie while carrying out research on the chronic rheumatic diseases under Professor Davidson. The remaining 134 cases were treated in the Royal Infirmary, Edinburgh, and were selected because the data in the case records were sufficiently detailed to give the requisite information required for the investigation.

It has to be noted that the hospitals in which these cases were treated admit children under the age of twelve only in exceptional circumstances, and thus no case of rheumatoid arthritis occurring before this age is included in this survey.

The analysis was undertaken to obtain information on the following points:

1. Sex incidence.
2. Age of onset.
3. Incidence of a history of preceding infection.
4. Incidence of a chronic focus of infection.
5. The relationship of pregnancy, childbirth, and the menopause to the onset of the disease.
6. Occupation of the affected person.
7. Joint (or joints) first involved.
8. The relationship between the duration of the disease and its severity on admission to hospital.

1. Sex Incidence

In the 388 cases 270 (69·5 per cent.) were females, 118 (30·5 per cent.) were males—*i.e.*, a ratio of 2·3 females to 1 male. (From Table II. it can be seen that while there is a small preponderance of females over males in Scotland it cannot account for the higher incidence of the disease in females.)

The ratio of 2·3 to 1 is in keeping with the figures obtained in the surveys by Munroe, Osgood and Pemberton, and Comroe, but is lower than those given by Copeman and Bach.

2. Age at Onset

In Table I. is given the age of onset in ten-year periods in the two sexes.

Table I.—Age of Onset by Age and Sex

Age.	Male.		Female.		Total.	
	No. of Cases.	*Per-centage.*	*No. of Cases.*	*Per-centage.*	*No. of Cases.*	*Per-centage.*
12–14	1	0·8	10	3·6	11	2·8
15–24	11	9·3	50	18·4	61	15·7
25–34	28	23·8	45	16·6	73	18·8
35–44	31	26·3	76	27·7	107	27·6
45–54	27	22·9	56	21·6	83	21·4
55–64	18	15·2	26	9·6	44	11·3
65–74	2	1·6	7	2·6	9	2·3
Total	118	99·9	270	100·1	388	99·4

Average of Onset

Males.	*Females.*	*Both.*
42	39	40

From the above table it can be seen that:

(*a*) The average age of onset in males was 42, in females was 39, and in the whole series 40.

(*b*) The general trend of the age of onset of both males and females corresponds fairly closely, 73 per cent. of the male cases and 66 per cent. of the female cases occurring in the age period 25 to 54.

(*c*) 49 per cent. of the cases occurred between the age period 35 to 54.

(*d*) The percentage of cases with the age of onset between the ages 12 to 24 is more than twice as high in the females as in the males; this is in keeping with the clinical impression that when rheumatoid arthritis occurs in the young the female is much more likely to be affected.

Before considering whether those figures have any significance in relation to the pathogenesis of the disease it is necessary to take into account the distribution of the total population in similar age periods. Table II. gives the distribution of both sexes of the population of Scotland in the relevant age periods for the year 1938. The figures were obtained from the Annual Report of the Registrar-General for

Scotland, 1938, and the year 1938 was chosen as being the middle year of the period 1935-40. The figures for the whole of Scotland had to be taken, as there are no figures for such areas as the east and south-east or north-east of Scotland, the main areas from which the cases under discussion were drawn. This is justifiable, as there is no indication that the age period distribution of the population in these areas is in any way different from the distribution in Scotland as a whole.

TABLE II.—ESTIMATED POPULATION OF SCOTLAND BY AGE AND SEX, 1938

Age.	*Both Sexes.*	*Males.*	*Females.*
15–24	859,100	430,900	428,200
25–34	804,300	391,800	412,500
35–44	666,200	309,600	356,600
45–54	554,300	252,900	301,400
55–64	468,900	219,400	249,500
65–74	290,200	133,400	156,800
Total	3,643,000	1,738,000	1,905,000

It might be argued that the variation of the population in each age group would account for the variation in the number of cases found in these groups as in Table I. Starting from this hypothesis for any given number of total cases the expected number in each age group can be calculated.

Table III. compares the number of cases actually present against the " expected " number in each age group in both sexes.

TABLE III.—COMPARISON BETWEEN THE NUMBER OF FOUND AND EXPECTED CASES BY AGE AND SEX

Age.	*Male.*		*Female.*		*Total.*	
	Found.	*Expected.*	*Found.*	*Expected.*	*Found.*	*Expected.*
15–24	11	29	50	58	61	87
25–34	28	26	45	57	73	83
35–44	31	21	76	49	107	70
45–54	27	17	56	41	83	58
55–64	18	15	26	34	44	49
65–74	2	9	7	21	9	30

Applying the chi-square test of significance to these figures it can be shown that the variation between the number of expected and found cases is significant. This means that some factor or factors other than the age distribution of population must be present to account for the number of cases in each group.

From Tables I. and II. can be calculated the relative incidence of the disease in each age group. This allows a direct comparison to be made of the incidence in one age group with another, thus eliminating the factor of the variation of the population in these groups. With the figures at my disposal a true incidence rate cannot be given, as neither the population of the districts from which the cases are drawn nor the number of all the cases of rheumatoid arthritis occurring in these districts is known. Therefore the calculation of such a " relative " incidence rate per 1,000,000 persons in each age group is the most satisfactory method available.

TABLE IV.—THE RELATIVE INCIDENCE RATE PER 1,000,000 BY AGE AND SEX

Age.	*Male.*	*Female.*	*Total.*
15–24	25·5	116·4	71·0
25–34	71·5	109·3	90·8
35–44	100·1	213·1	160·6
45–54	105·2	185·8	149·7
55–64	83·9	104·2	93·8
65–74	15·0	44·6	34·5

From Table IV. it can be seen that:

(*a*) In the males the highest incidence occurs between the ages 35 to 54, but that there is no great difference in any age group from 25 to 64.

(*b*) In males the disease is as common between the ages 55 to 64 as between 25 to 34, and three to four times more common as between the 15 to 24.

(*c*) In females the incidence is doubled between the ages 35 to 54 as compared with the age period 25 to 34 and 55 to 64.

(*d*) In females the incidence of the disease between 55 to 64 is almost as great as in either of the age periods 15 to 24 or 25 to 34. Thus the widely accepted clinical view that rheumatoid arthritis is mainly a disease of young women is not supported by these findings.

(*e*) If the disease does occur before the age of 25 the incidence is four to five times greater in the female than the male.

3. INCIDENCE OF A HISTORY OF PRECEDING INFECTION

In this analysis only those infections which occurred within two months prior to the onset of symptoms were considered significant. The types of infection met with were upper respiratory tract infection, sinusitis, teeth abscesses, pyelitis, phlebitis, etc.

Table V. shows the distribution of a history of preceding infection by age and sex.

TABLE V.—DISTRIBUTION OF A HISTORY OF PRECEDING INFECTION BY AGE AND SEX

Age.	Males.			Females.			Total.		
	No. of Cases.	Preceding Infection.	Per Cent.	No. of Cases.	Preceding Infection.	Per Cent.	No. of Cases.	Preceding Infection.	Per Cent.
12–14 ..	1	1	(100)	10	1	10·0	11	2	18·0
15–24 ..	11	1	9·1	50	13	26·0	61	14	23·0
25–34 ..	28	3	10·7	45	13	28·8	73	16	36·4
35–44 ..	31	5	16·1	76	17	22·4	107	22	20·5
45–54 ..	28	2	7·1	56	12	21·4	83	14	16·9
55–64 ..	18	3	16·6	26	1	4·0	44	4	9·1
65–74 ..	2	0	—	7	0	—	9	0	—
Total ..	118	15	11·8	270	57	21·0	388	72	18·3

A definite history of preceding infection was obtained in only 15 cases out of 118 males (11·8 per cent.) and in 57 out of 270 females (21 per cent.). The incidence was fairly evenly distributed in both sexes throughout the age periods 25 to 54, a period which includes 70 per cent. of the cases. This even distribution is more striking when both male and female cases are considered together. The maximum incidence of a history of preceding infection occurs in the age period 25 to 34.

On the other hand, after the age of 55 the incidence of a history of preceding infection is much lower than for the whole group, 4 out of 53 (7·5 per cent.), while the incidence in the age period 12 to 34 is 42 out of 145 cases (30 per cent.).

These findings are of some interest, since they support to some extent the view that in young persons infection is of greater ætiological importance than in the old.

However, an incidence of a history of preceding infection of only 18·3 per cent. is small, and accordingly it is unwise to draw definite conclusions from these figures.

4. THE INCIDENCE OF FOCAL SEPSIS

Table VI. gives the number of cases in which a focus of infection was found, by age and sex.

From the following table it can be seen that:

(*a*) A focus of infection was found in 147 out of 388 cases—*i.e.*, 38 per cent.

(*b*) In the elderly patients of over 55 years of age the incidence of focal sepsis was 8 out of 53 cases (15 per cent.), while in persons younger than 25 focal sepsis was found in 34 out of 72 cases (47 per cent.).

TABLE VI.—DISTRIBUTION BY AGE AND SEX OF CASES IN WHICH A FOCUS OF INFECTION WAS FOUND

Age.	Male.			Female.			Total.		
	No. of Cases.	*Focal Sepsis.*	*Per Cent.*	*No. of Cases.*	*Focal Sepsis.*	*Per Cent.*	*No. of Cases.*	*Focal Sepsis.*	*Per Cent.*
12–14 ..	1	1	(100)	10	4	40·0	11	5	45·0
15–24 ..	11	7	50·0	50	22	44·4	61	29	47·5
25–34 ..	28	12	42·8	45	26	57·7	73	38	52·0
35–44 ..	31	12	38·7	76	27	35·5	107	39	37·8
45–54 ..	27	9	33·3	56	19	34·0	83	28	33·7
55–64 ..	18	5	27·7	26	3	11·5	44	8	18·0
65–74 ..	2	0	—	7	0	—	9	0	—
Total ..	118	46	39·0	270	101	37·4	388	147	38·0

These findings and the deductions to be drawn from them correspond to those discussed under the incidence of a history of preceding infection.

The sites of infection were as follows:

Tonsils	97
Teeth	32
Sinuses	13
Uro-genital tract	11
Aural	4
Breast	3
Veins	3
Lung	3
Gall-bladder	1

The commonest sites for foci of infection were found to be the mouth and upper respiratory passages. This is in keeping with the age distribution of foci of infection shown in Table VI., for it is widely recognised that such infections are commoner in childhood and adolescence than in adult life.

Conclusions

An investigation into the part played by infection in the ætiology of rheumatoid arthritis is very difficult. In the case of a history of preceding infection, if a patient comes to hospital for the first time two to three years after the onset of the disease he may have forgotten a transient sore throat or cold which occurred three to four weeks before the onset of the disease. This delay, unavoidable in a disease usually insidious in onset, will tend to keep unduly low the number of cases giving a history of preceding infection.

As regards investigations into the foci of infection this delay has also to be considered, as infected tonsils or dental abscesses may have

been eradicated before the patient reports for treatment for the arthritis.

I can find no reference in the literature to the incidence of foci of infection in the normal healthy population. Without such a figure for comparison no conclusions can be drawn from the figures found in this investigation. If, however, infection were to play a major rôle in the pathogenesis of the disease one would expect a high incidence of infection in cases of rheumatoid arthritis, and the maximum incidence of such an infection should fall within the same age period as the maximum incidence of the onset of the disease.

The incidence of 18·3 per cent. for a history of preceding infection and of 38 per cent. for a focus of infection in this investigation appears to be too low to be significant.

Also the maximum incidence of the onset of rheumatoid arthritis was found between 35 to 54, whereas the maximum incidence of both a history of preceding infection and of a focus of infection was found between the ages 15 to 34.

Accordingly it would appear that if infection is important it is probably not the frequency or the severity of the infection that is significant, but perhaps some other factor such as the abnormal response of the patient to infection.

5. (*a*) The Relationship of Pregnancy to the Onset of Arthritis

The relationship of pregnancy to the onset of arthritis was investigated by noting the number of cases in which the onset of the disease or a relapse occurred either during pregnancy or within six months of parturition.

In no case did arthritis manifest itself during pregnancy.

There were 27 cases in which symptoms developed within six months after parturition—*i.e.*, 10 per cent. of all female cases. As pregnancy occurred only in the period 20 to 40 in the cases investigated, the true incidence is 27 out of 107 cases—*i.e.*, 25 per cent.

However, in 25 of the 27 cases either a history of preceding infection was obtained or a focus of infection found.

Of these 27 cases 15 had further pregnancies subsequent to the onset of the arthritis. In only three cases did subsequent child-bearing produce deterioration of the arthritis. In the other twelve there were no data stating whether or not the arthritis improved during pregnancy.

Conclusions

Although these figures are too small to draw any certain conclusions, they indicate that pregnancy does not appear to play any specific rôle in the ætiology of rheumatoid arthritis.

5. (*b*) The Relationship of the Menopause to the Onset of Arthritis

The changes in the metabolism of the body and the psychological outlook of the person associated with the menopause occur over a wide period both before and after the cessation of menstruation.

In this analysis all cases which developed arthritic symptoms in the period two years before to two years after the cessation of menstruation were noted.

Nineteen such cases were found—*i.e.*, 7 per cent. of all female cases. In the series the menopause occurred only in the period 35 to 54; thus the true incidence was 19 out of 132 cases—*i.e.*, 14·4 per cent.

In 11 of those cases either a history of preceding infection was obtained or a focus of infection found.

Conclusions

From the above data the figure $\frac{4}{20}$ gives an approximation of the chance association between the onset of arthritis and the cessation of menstruation. The actual percentage of 14·4 per cent. is lower than what might have been expected by coincidence, and this would indicate that the menopause does not tend to precipitate the onset of rheumatoid arthritis.

6. Occupation

The undernoted figures are based on the 288 cases drawn from the Edinburgh hospitals:

Domestic duties	165
Casual labouring work	13
Retail trade	13
Ploughman	10
Miner	9
Engineer	9
Typist	9
Joiner	8
Baker	4
Distillery worker	4
Printer	4
Mason	4
Railway worker	3
Bricklayer	3
Sailor	3
Schoolgirl	3
Nurse	3
Commercial traveller	2
Waitress	2
Car conductor	2
Plumber	2
Painter	2
Laundry worker	2
Blacksmith	1
Not stated	8
	288

The only point of interest in the above list is the great predominance of cases carrying out domestic duties. This is not surprising considering that 195 of the 288 cases were females and the great majority of women of the hospital class in the age period 25 to 54 are occupied with domestic duties.

7. Site of Commencement of the Disease as indicated by the First Joint Affected

Table VII.

Joint Affected.	*Male.*		*Female.*		*Total.*	
	No. of Cases.	*Per Cent.*	*No. of Cases.*	*Per Cent.*	*No of Cases.*	*Per Cent.*
Fingers	24	26	75	38	99	35
Knees	17	18	50	26	67	21
Wrists	13	14	25	13	38	13
Feet	9	10	21	11	30	11
Ankles	18	19	10	5	28	10
Shoulders	8	9	5	2	13	5
Elbows	3	3	7	4	10	4
Hips	1	1	2	1	3	1

From the above table it can be seen that the disease started in the fingers in 38 per cent. of the females as compared with 26 per cent. of the males. If the hypothesis is accepted that the joints most likely to be affected are those submitted to the greatest strain, then the higher incidence of the disease starting in the interphalangeal and metacarpal-phalangeal joints in the female might be explained.

The frequency with which the arthritis started in joints other than the fingers and wrists is considerably higher (52 per cent.) than a study of the literature would lead one to expect.

8. The Relationship between the Duration of the Disease and its Severity

The 288 cases admitted to the Edinburgh hospitals were used in this investigation.

The cases were divided according to the state of the disease into the following groups:

Group 1.—Peri-articular swelling with stiffness, but only little limitation of movement.

Group 2.—Peri-articular swelling with more marked limitation of movement than in Group 1, but no evidence of ankylosis, and still in employment.

GROUP 3.—Fixation of joints, flexion deformities, and inability or great difficulty in continuing in employment.

GROUP 4.—Gross deformities with patient either bedridden or severely crippled.

According to this classification the cases were distributed as follows:

Group 1	.. ..	34 (11·9 per cent.)
,, 2	.. ..	116 (40·3 ,,)
,, 3	.. ..	109 (37·5 ,,)
,, 4	.. ..	29 (10·1 ,,)

The average duration of the disease in each group was:

Group 1	.. ..	1·3 years
,, 2	.. ..	2·4 ,,
,, 3	.. ..	5·0 ,,
,, 4	.. ..	7·0 ,,

47·5 per cent. of the cases fell into Groups 3 and 4. Thus nearly half the cases were crippled before hospital treatment was started.

This is brought out more strikingly in Table VIII., in which the cases were divided according to the duration of the disease into:

(*a*) Up to 6 months.
(*b*) Between 6 months and 1 year.
(*c*) 1 to 3 years.
(*d*) 4 to 6 years.
(*e*) 7 to 9 years.
(*f*) 10 years and over.

The cases in each of these divisions were then placed in their respective groups according to the severity of the disease, as shown in Table VIII.

TABLE VIII.

Duration of Disease.	*No. of Cases.*	*Group 1.*		*Group 2.*		*Group 3.*		*Group 4.*	
		No.	*Per Cent.*	*No.*	*Per Cent.*	*No.*	*Per Cent.*	*No.*	*Per Cent.*
Up to 6 mths.	37	14	38	16	43	6	16	1	3
6 months to 1 year ..	30	10	33	16	53	3	10	1	3
1 to 3 years ..	107	8	7	50	47	40	37	9	9
4 to 6 years ..	50	0	—	16	32	28	56	6	12
7 to 9 years ..	20	0	—	6	30	9	45	5	45
10 years and over ..	44	2	4·5	12	27	23	52	7	16

From this table it can be seen that:

(*a*) During the first year of the disease 83·6 per cent. of the cases are in either Group 1 or 2.

(*b*) By 1 to 3 years only 54 per cent. are in Group 1 or 2.

(*c*) After the disease has lasted for ten years or more only 31·5 per cent. fall into the first two groups.

Conclusions

From these figures it can be said that as a general rule the longer the disease has existed the more severe it is. The outlook for patients in Groups 3 and 4 is very much worse than for those in Groups 1 and 2, and the importance of early and thorough treatment is obvious.

Summary

1. A survey of 388 cases of rheumatoid arthritis is reported.

2. In this series the disease was found to be two to three times more common in females than males.

3. The maximum incidence of age of onset occurs between 35 and 54 (49 per cent.). In males and females the incidence between the ages of 55 and 64 is approximately the same as between 25 and 34 (Table IV.).

4. A history of preceding infection was obtained in 72 cases out of 388 (18·3 per cent.).

5. The incidence of focal sepsis was 147 out of 388 cases (38 per cent.).

6. No case of arthritis developed during pregnancy, while 27 cases of the 107 patients in the child-bearing period age (25 per cent.) occurred within six months of parturition.

7. Nineteen cases out of 132 (14·4 per cent.) between the ages 35 to 54 developed symptoms of arthritis within two years of cessation of menstruation.

8. The disease had been present for five years or more in 47·6 per cent. of the cases when first seen. The degree of crippling was found to be closely related to the duration of the disease.

I wish to express my thanks to Dr. Clark, M.O.H., Edinburgh, for allowing me to use the material from the Municipal Hospitals, Edinburgh; the Physicians of the Royal Infirmary, Edinburgh, for giving me access to their case records; Dr. J. J. R. Duthie for putting at my disposal the cases he had investigated in Aberdeen; and particularly to Professor L. S. P. Davidson for his criticism and advice.

A STUDY OF LIVER FUNCTION AND PLASMA VOLUME IN CHRONIC RHEUMATISM BY MEANS OF PHENOL-TETRABROM-PHTHALEIN SODIUM SULPHONATE*

By G. L. ROBINSON

(From the Research Laboratory of the Devonshire Royal Hospital, Buxton.)

I. Introduction

The idea that the tendency to develop arthritic disease is " undoubtedly a hepatic deficiency " (Bezançon and Weil, 1938) not only still persists but has gained some support from the laboratory. Two reports (both labelled preliminary, though both devoid of issue) have described hepatic function among assortments of chronic rheumatics as impaired: one author (Watson, 1928) used a salicylate excretion test, while the other (Miller, 1935) estimated lævulose tolerance. In the case of rheumatoid arthritis only, a decreased tolerance for glucose has been remarked more than once, and a recent determination (Andrews and Muether, 1941) of the arteriovenous difference of blood-glucose level in this disease discounts any explanation in terms of accelerated blood flow, favouring an actual fall in the glycogenic power of the liver, which might, however, be either hepatic or endocrine in origin. An investigation of liver function (Rawls, Weiss and Collins, 1939), in which intravenously injected azorubin was recovered by duodenal tube, resulted in 60 per cent. abnormal excretions among fifty unselected cases of rheumatoid arthritis. This abnormality was held to lie not always in delayed, but sometimes in accelerated transference of dye into the bile. On the clinical side, a collection has been made (Hench, 1938-40) of over seventy cases of " atrophic arthritis " and " primary fibrositis" in which the chance concurrence of jaundice caused dramatic though temporary remissions of rheumatic symptoms. This appears to contradict the foregoing results, and might even be interpreted to mean that the rheumatic liver is over-efficient, a state of affairs also suggested by those " abnormal " azorubin excretions which were accelerated. Again, the blood protein in rheumatoid arthritis is raised, whilst in liver deficiency it is lowered. The finding of raised blood volumes by the Congo red method (Sparks and Haden, 1932) in twenty-six cases of rheumatoid arthritis might also be made to fit a picture of hepatic hyperfunction by assuming that the dye

* Based on a thesis for the degree of M.D. (University of Cambridge), by permission of the Regius Professor of Medicine.

had not been overdiluted by excess of plasma, but removed by over-active Kupffer cells. In the present work, the liver test dye phenol-tetrabrom-phthalein sodium sulphonate (" bromsulphalein ") has been used in such a way as to throw some light both on liver function and on plasma volume in chronic rheumatism.

II. Technical Procedure

Preliminary experiments established the following points: (1) that bromsulphalein added *in vitro* to the blood of normal or rheumatoid subjects does not enter the red corpuscles; (2) that bromsulphalein is removed from plasma with the protein in the Folin-Wu, but remains with the liquid in alcohol or acetone precipitation; (3) that bromsulphalein dissolved in plasma will not pass a collodion membrane in four days, but dissolved in saline or 5 per cent. peptone will diffuse at once, reaching equilibrium in about twelve hours; (4) that solutions of bromsulphalein in dilute ammonia give a well defined absorption band, centred at 583 mμ, when examined in a Hilger spectrophotometer.

The following method was developed to extract the dye, free from opacities and protein, from blood samples for spectrophotometric estimation. To 3 ml. distilled water in a 15-ml. centrifuge tube add 8 ml. acetone and invert to mix, then 1 ml. plasma and invert three times. Centrifuge 3 to 4 minutes at 2 to 3 thousand revolutions per minute. With a 9-ml. pipette, the tip just above packed precipitate, withdraw 9 ml. fluid by sucking steadily to above mark and draining down. Run this fluid into a similar tube containing 1 ml. distilled water, add 2 ml. chloroform, stopper by thumb and give about fifty vigorous horizontal shakes. Centrifuge as before. Transfer the whole supernatant layer by teat pipette to 20-ml. volumetric flask. Dilute with distilled water, add 1 ml. ·880 ammonia, then dilute to mark with distilled water and mix well. Read in a 10-cm. cell (15-ml. capacity) in the spectrophotometer from half to one hour later. The formula, determined by plotting known concentrations of dye in plasma, is:

$$x = 3{\cdot}5\ (D - 0{\cdot}25),$$

where x is the plasma concentration of dye in mg. per 100 ml. and D is the extinction coefficient at 583 mμ read directly on the scale.

It was now possible to follow the fate of intravenously injected dye by repeated sampling at short intervals, thus producing bromsulphalein tolerance curves (Fig. 1) which showed maxima at 1·25 minutes after injection and a slowing of the initially uniform removal rate after about six minutes. A three-sample procedure was therefore adopted as standard for the clinical side of the testing: the first sample to give the peak value attained at 1·25 minutes, the second at 2·5 minutes to fix the initial rate of fall where the graph is rectilinear

and steep, the third at 7·25 minutes for estimation of the removal rate over the whole sensitive period before the rate becomes slow.

After a gentle walk of about two minutes, the patient is seated beside a table in such a position that either arm can be laid across the corner of it in comfort. An accurate syringe is then charged with the required dose (3·5 mg. per kg. body weight was used in the present work) of 5 per cent. solution of bromsulphalein, and three other syringes (5 or 10 ml.) are prepared by rinsing with sterile saline and laid ready in a row on the table, the first only bearing a SWG 20 needle, while the third contains 1 ml. sterile saline. A watch with a seconds hand and three 5-ml. centrifuge tubes, each containing one drop of saturated potassium oxalate solution, are also placed handy. The injection of the dye is made to last for a period of 25 ± 5 seconds after release of the tourniquet on entering the vein, and the arm subsequently held raised for one minute and then lowered into the lap. As soon as the injection is over, the other arm is placed upon the table, tourniquet applied, vein entered and tourniquet released, this process being completed in well under 30 seconds. At exactly one minute after the end of the injection blood is drawn into the syringe at such a pace that 5 ml. are obtained in 30 seconds, the average timing of this sample being therefore 1·25 minutes. The syringe is then detached, handed to the assistant, who ejects the blood into the first oxalated tube and mixes it, and the second syringe is fitted to the needle. The second sample is drawn in the same way from 2·25 to 2·75 minutes, being therefore timed at 2·50 minutes after the end of the injection. On attaching the third syringe to the needle, 1 ml. sterile saline is injected from it into the vein in order to prevent clotting in the needle during the longer wait until the third sample, timed at 7·25 minutes, is drawn.

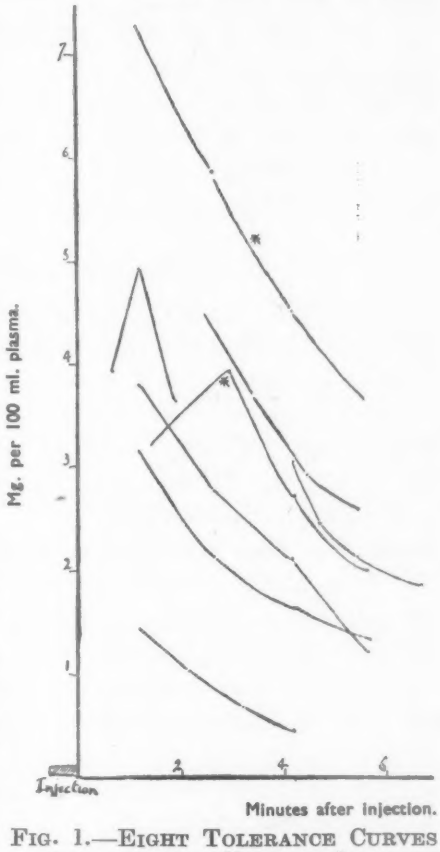


FIG. 1.—EIGHT TOLERANCE CURVES OBTAINED FROM VARIOUS SUBJECTS USING VARIOUS DOSES AND SAMPLE TIMES.

In order to calculate the plasma volume by this method, it is assumed that the same amount of dye is removed during the first 1·25 minutes after the end of injection as during the second, which figure is given

by the difference in concentration between first and second samples. In other words, the steep straight line of the early part of the tolerance curve is produced backwards to cut the ordinate at a concentration which would have been attained had not the dye been undergoing removal at the determined rate. Plasma volume is then found by dividing this theoretical maximum concentration (mg. per 100 ml.) into one hundred times the weight (mg.) of dye administered. It will be seen from ensuing tables that absolute values found for normals are not much below the orthodox 50 ml. plasma per kg. body weight given by most dye tests of blood volume and assumed in calibration of the comparator tubes used in the ordinary bromsulphalein test of liver function (Rosenthal and White, 1925).

No ill effects of any kind were ever observed to follow intravenous injection of bromsulphalein.

III. Discussion of Procedure

A certain number of subjects exhibited " delayed " curves in which the concentration of dye in the second sample equalled or even exceeded that in the first. Such results did not occur with cases treated in bed or sitting in wheeled chairs, but they seemed to come particularly from those ambulant subjects who had waited for some time before being tested. It was only towards the end of the series that the preliminary two-minute stroll was adopted, eliminating further anomalies; thus a number of delayed curves are included in the tables below, in which, in the absence of a peak concentration at 1·25 minutes, no calculation of plasma volume was possible, and in which dye retention could only be determined over the 4·75 minute period between second and third samples. A delayed curve is shown, marked with an asterisk, in Fig. 1, the other curve so marked being from the same subject (a healthy engine-driver aged 54 suffering from sciatica) using a 1·5 times larger dose of dye one week later.

To express numerically the ability of the liver to remove dye from the circulation it is not enough simply to measure the crude removal rate in mg. per 100 ml., for this rate varies with the concentration of dye in the plasma, as is shown by comparing the slopes of the uppermost and lowermost curves in Fig. 1. In theory, the concentrations of dye in the plasma of different subjects can be equated by the use of a dosage proportional to body weight; but in practice, particularly in the diseased, plasma volume is not always paralleled by body weight. It is perhaps because these two factors (*i.e.*, dependence of removal rate on concentration and lack of constant relation between plasma volume and body weight) act in opposition to each other that they have been neglected in the orthodox bromsulphalein test; but variation in the hepatic removal rate of dye is not of such a degree as rapidly to equate varying concentrations in the blood stream.

Therefore in this work the " index of hepatic efficiency " has been obtained by expressing the rate of removal (mg. per 100 ml. per min.) as a percentage of the concentration of dye in the plasma (mg. per 100 ml.) at the beginning of the period over which removal rate is measured. In order to include delayed curves, this index has been calculated for the period between second and third samples (4·75 mins.) as well as for that between first and third (6 mins.).

IV. Tables of Results

The data obtained by testing are set out in eleven numbered columns in a series of tables.

Column 1 gives the age of the subject in years.

Column 2 gives the weight of the subject in kg.

Column 3 gives the suspension stability of the blood. The figure expresses the percentage of the blood volume occupied by the red cells at the end of one hour's sedimenting of 5 ml. oxalated blood in a centrifuge tube. The method has been adopted as standard by several rheumatic hospitals (Collins *et al.*, 1939).

Column 4 gives the percentage of the blood volume occupied by the packed red cells.

Column 5 gives the plasma protein percentage, estimated by the Kjeldahl method.

Column 6 gives the plasma volume in ml. per kg. body weight, obtained by the bromsulphalein method.

Column 7 gives the blood volume in ml. per kg. body weight.

Column 8 gives the removal rate of bromsulphalein from the blood stream in mg. per 100 ml. per minute, over a 6-minute interval from 1·25 to 7·25 minutes after injection.

Column 9 gives the 6-minute index of hepatic efficiency, obtained by expressing the 6-minute removal rate as a percentage of the dye concentration in the first sample.

Column 10 gives the removal rate over a 4·75 minute interval from 2·5 to 7·25 minutes after injection.

Column 11 gives the 4·75 minute index of hepatic efficiency—*i.e.*, the 4·75 minute rate expressed as percentage of dye concentration in the second sample.

Table I comprises the results obtained with thirteen female controls by the three-sample procedure and the acetone extraction, using a dose of 3·5 mg. per kg. body weight. It will be seen that these cases are anæmic, with a packed red cell volume averaging only 37 per cent., whereas the normal figure for oxalated female blood is 42 per cent. (Collins *et al.*, 1939). This anæmia is that of the " hospital class," related to income rather than minor rheumatic trouble: number 76, for instance, attending for massage with a healed laceration of the fore-arm, shows no less anæmia than the rest.

TABLE I

No. of Column :	1	2	3	4	5	6	7	8	9	10	11
67. Sciatica	40	54·3	80	37	5·7	39·4	62·2	0·77	10·5	0·66	11·2
68. Sciatica	44	52·9	86	39	6·3	48·5	79·5	0·67	11·6	0·58	12·7
69. Sciatica	53	52·0	60	34	5·6	48·6	73·6	0·69	11·0	0·65	12·5
70. Sciatica	31	50·0	88	40	6·1	48·8	81·3	0·67	11·1	0·60	12·3
71. Sciatica	69	71·4	82	37	5·7	29·8	47·3	1·08	11·4	0·88	12·3
72. Lumbago	21	48·6	71	36	6·2	—	—	—	—	0·65	13·8
73. Sciatica	30	54·3	90	35	5·5	45·6	70·1	0·68	10·7	0·58	11·6
74. Fibrositis	66	56·0	84	38	5·8	—	—	—	—	0·51	9·6
75. Fibrositis	18	50·0	75	32	6·3	52·8	77·6	0·62	10·9	0·58	12·3
76. Normal	41	51·4	90	36	5·7	42·2	65·9	0·68	10·4	0·49	10·2
77. Lumbago	26	45·5	93	37	5·7	55·2	87·6	0·56	11·0	0·44	11·8
78. Sciatica	38	58·6	96	38	5·3	50·0	80·6	0·62	10·4	0·57	11·1
79. Fibrositis	39	44·3	88	36	5·9	49·3	77·0	0·63	10·7	0·55	11·6
Average ..	40	53·0	83	37	5·9	46·4	73·0	0·70	10·9	0·59	11·8

TABLE II.—FINDINGS IN TWENTY-ONE FEMALE CASES OF RHEUMATOID ARTHRITIS (TWO REPEATS BEING INCLUDED) WHICH WERE SELECTED AS TYPICAL OF THE DISEASE.

No. of Column:	1	2	3	4	5	6	7	8	9	10	11
80	29	37·2	55	29	6·5	69·9	98·5	0·47	11·3	0·41	12·3
81	39	53·5	54	31	6·1	49·3	71·4	0·60	10·1	0·52	10·8
(1)	40	48·6	54	33	6·3	56·9	84·9	0·49	8·9	0·48	9·9
82	25	52·0	47	32	6·2	54·6	80·3	0·66	13·5	0·55	16·2
83	30	41·4	52	30	6·0	68·1	97·3	0·49	12·8	0·36	13·3
(2)	30	44·0	62	38	6·9	57·2	92·3	0·55	10·8	0·49	12·7
84	23	53·0	45	32	6·5	53·8	79·1	0·62	11·8	0·53	13·2
85	53	41·5	45	29	6·4	66·5	93·7	0·45	10·3	0·39	11·0
86	53	47·2	46	34	5·7	49·2	74·5	0·61	9·6	0·45	9·2
87	31	65·7	53	34	6·3	59·7	90·5	0·46	9·4	0·33	8·5
88	28	40·0	52	—	6·3	—	—	—	—	0·43	10·2
89	27	47·2	50	35	6·2	63·1	97·1	0·55	12·1	0·49	13·7
90	37	43·5	49	32	6·4	66·4	97·6	0·50	11·4	0·44	12·7
91	32	44·3	62	33	6·4	—	—	—	—	0·45	11·2
92	33	42·5	44	32	7·4	63·3	93·1	0·41	8·8	0·43	9·1
93	39	37·2	46	36	6·6	70·7	110·5	0·43	10·4	0·37	11·1
94	47	38·6	38	26	6·9	76·3	103·1	0·34	8·0	0·35	9·0
95	35	44·0	47	31	6·6	65·0	94·2	0·46	9·4	0·41	9·9
96	22	50·0	54	29	6·3	66·8	94·1	0·51	10·8	0·53	12·6
97	28	30·0	48	28	6·6	71·1	98·7	0·58	9·6	0·53	10·4
98	37	36·0	49	29	7·8	67·7	95·4	0·56	9·1	0·49	9·7
Average	34	44·6	50	32	6·5	62·9	91·9	0·51	10·4	0·45	11·4

(1) Same subject as 81, worse, 1 year later.
(2) Same subject as 83, improved, 5 weeks later.

Twenty-four male controls are listed in Table III, 8 cases of typical subacute rheumatism in Table IV.

TABLE III

No. of Column :	1	2	3	4	5	6	7	8	9	10	11
99. Sciatica	33	60·0	88	38	5·8	51·7	83·4	0·57	12·0	0·45	14·5
100. Sciatica	63	61·4	74	35	5·5	53·5	82·3	0·65	11·4	0·64	13·2
101. Sciatica	52	64·3	68	34	5·9	41·1	62·3	0·86	12·7	0·72	14·2
102. Sciatica	39	70·0	83	38	6·3	52·6	84·8	0·65	11·6	0·60	13·2
103. Sciatica	30	60·0	97	41	5·3	48·7	82·6	0·70	11·6	0·64	13·2
104. Sciatica	35	68·6	97	41	5·6	43·1	73·0	0·74	11·6	0·57	12·3
105. Sciatica	40	63·0	90	38	6·1	48·5	78·2	0·69	11·4	0·63	12·9
106. Sciatica	31	70·0	94	37	5·6	54·0	85·7	0·63	11·3	0·61	12·9
107. Sciatica	42	65·7	95	36	5·7	53·2	83·1	0·58	11·0	0·46	11·5
108. Sciatica	32	68·0	90	39	5·6	52·3	85·7	0·68	11·8	0·65	13·6
109. Sciatica	22	67·2	95	44	6·1	—	—	—	—	0·63	15·1
110. Sciatica	45	74·3	95	43	5·5	49·5	86·8	0·68	11·0	0·66	12·6
111. Sciatica	25	60·0	98	44	5·7	43·1	77·0	0·82	13·0	0·66	15·0
112. Sciatica	38	64·3	95	40	5·3	40·4	67·3	0·86	13·5	0·60	14·7
113. Lumbago	49	58·6	94	40	5·5	—	—	—	—	0·57	14·2
114. Normal	24	63·0	95	43	5·6	55·6	97·5	0·63	11·7	0·62	13·6
115. Normal	35	60·0	96	37	5·6	—	—	—	—	0·51	12·5
116. Normal	38	70·0	90	43	5·2	—	—	—	—	0·68	13·7
117. Normal	21	67·0	97	40	5·5	47·3	78·8	0·69	11·5	0·57	12·5
118. Normal	29	61·4	97	42	5·4	51·3	88·4	0·70	13·3	0·56	15·0
119. Normal	48	73·0	95	42	5·6	43·8	75·5	0·61	9·6	0·44	9·2
120. Fibrositis	46	73·0	92	39	5·7	42·3	69·3	0·64	10·1	0·40	9·2
121. Fibrositis	42	66·0	90	35	5·7	50·7	78·0	0·66	11·1	0·63	12·9
122. Pleurodynia	33	55·7	89	41	6·2	45·5	77·1	0·73	11·8	0·60	12·8
Average	37	65·2	91	40	5·7	48·4	79·9	0·69	11·7	0·59	12·3

TABLE IV.—SUBACUTE RHEUMATISM

No. of Column :	1	2	3	4	5	6	7	8	9	10	11
147. Female	24	60·0	82	34	5·2	55·8	84·5	—	—	0·53	15·0
148. Female	24	53·0	88	36	5·8	—	—	—	—	0·59	10·5
149. Female	19	70·0	78	37	5·6	53·0	84·1	—	—	0·59	12·2
150. Female	31	48·6	84	36	5·7	52·3	81·7	—	—	0·44	9·3
151. Female	33	45·7	51	35	5·9	—	—	—	—	0·37	9·2
152. Female	24	60·0	76	36	5·9	42·5	66·4	—	—	0·57	12·1
153. Male ..	27	68·6	76	40	5·8	45·0	75·0	—	—	0·67	14·9
154. Male ..	33	62·0	50	36	6·5	51·0	79·7	—	—	0·59	11·5

TABLE V.—SIX CASES OF MENOPAUSAL PERIARTICULAR FIBROSITIS

No. of Column :	1	2	3	4	5	6	7	8	9	10	11
135	61	50·0	61	33	5·9	48·5	72·4	0·61	10·6	0·51	11·1
136	42	65·0	58	34	5·9	50·0	70·5	0·58	9·5	0·55	10·5
137	53	53·0	52	37	7·0	38·5	61·1	0·83	12·2	0·58	12·5
138	56	81·5	70	33	6·1	53·1	79·2	0·47	9·4	0·41	9·9
139	46	50·0	58	32	5·9	—	—	—	—	0·45	9·2
140	55	41·4	85	37	5·5	41·6	66·0	0·75	11·2	0·55	11·4

TABLE VI.—SIX CASES OF OSTEO-ARTHRITIS

No. of Column :	1	2	3	4	5	6	7	8	9	10	11
141. Female	49	80·0	85	39	5·9	37·0	60·7	—	—	—	—
142. Female	38	57·2	89	42	5·8	41·4	71·4	—	—	—	—
143. Female	48	56·0	82	42	5·9	40·0	68·9	—	—	—	—
144. Male ..	46	57·2	94	47	5·8	47·9	90·5	—	—	—	—
145. Male ..	32	74·0	98	44	5·6	46·1	82·3	—	—	—	—
146. Male ..	60	75·0	78	39	5·8	44·4	72·8	—	—	—	—

TABLE VII.—FINALLY, THE RESULTS OF SEVEN SUBJECTS WHO FAINTED DURING THE TEST, TOGETHER WITH THOSE OF ONE CASE OF HEPATIC CIRRHOSIS, INCLUDED AS CONTROL (NO. 134)

No. of Column :	1	2	3	4	5	6	7	8	9	10	11
127. Male ..	25	61·5	92	39	5·8	52·0	85·2	0·38	6·0	0·41	6·8
128. Male ..	36	54·3	95	38	5·2	—	—	—	—	0·41	10·0
129. Male ..	20	73·0	95	42	5·5	52·6	90·7	0·47	8·2	0·39	8·2
130. Male ..	35	75·0	74	36	5·9	51·2	80·0	0·56	9·8	0·47	10·3
131. Male ..	27	53·0	77	40	5·9	—	—	—	—	0·39	9·5
132. Male ..	32	68·6	93	44	5·3	41·9	74·8	0·61	9·4	0·38	8·3
133. Female	37	51·4	66	29	6·5	52·1	73·5	0·49	8·7	0·38	8·5
134. Female	28	48·6	56	24	5·6	60·2	78·7	0·21	3·9	0·13	2·8

127, Lumbago; 128, 129, Sciatica; 130, Subacute rheumatism; 131, Ankylosing spondylitis; 132, Gout; 133, Arthritis of knees.

V. ANALYSIS OF RESULTS

A. Hepatic Efficiency.

As an example of the error involved by neglecting plasma volume in bromsulphalein testing, an article was found (Ezickson, 1939) in which the age and sex of the subjects were tabulated. The females from this table (p. 838) can be divided, taking the critical age as 45 years, into pre- and post-menopausal groups. The average dye retention in the younger group comes to 12·1 per cent., or little above

the normal value, given as 10 per cent.; but that in the older group, averaging 21 per cent., is double what it should be. This age difference is not a measure of hepatic inefficiency, but is due to the fact that the increased body weight of post-menopausal obesity is unaccompanied by a proportional increase in plasma volume, and thus a greater concentration of dye was induced in the plasma of these cases.

A comparison of the hepatic indices in Tables I and II fails to show any significant difference between female control (averages 10·9 and 11·8) and female rheumatoid subjects (10·4 and 11·4). It may be concluded, therefore, that no abnormality of liver function detectable by this test, neither over- nor under-activity, is associated with rheumatoid arthritis. As regards other forms of chronic rheumatic disease: normal hepatic efficiency was found in subacute rheumatism (Table IV), in menopausal periarticular fibrositis (Table V), and also, using an earlier modification of the bromsulphalein test, in numerous cases of osteo-arthritis; but in the case of gout (occasional cases found normal) and ankylosing spondylitis (occasional cases found slightly below normal) insufficient material was tested for conclusions to be drawn. Only typical cases were selected; for instance, a marked rise of antistreptolysin titre was present in the sera of the subacute rheumatics.

The method is sensitive enough to reveal that the male control cases show more active liver function (Table III, averages 11·7 and 13·2) than the females. Moreover, the suitability of the test to detect a minor degree of liver dysfunction, had it been present, is further indicated by the results obtained in cases of syncope.

The occurrence of fainting when blood samples are drawn can be reduced to a rarity; but it cannot be abolished altogether, and is especially favoured by the sitting posture. In the first case of this kind it was noticed that the hepatic indices showed depression. It was found possible subsequently to encourage six further faints from suitable soil (*e.g.*, by drawing attention to the blood entering the syringe). All were typical examples of vaso-vagal syndrome (Lewis, 1932), salivation, perspiration, pallor, nausea and bradycardia leading either to swimminess in the head or complete unconsciousness. The results are given in Table VII, where the average 4·75 minute index for the six males is seen to be 8·8, as against an average control index (Table III) of 13·3. Thus the index of hepatic efficiency is depressed by temporary circulatory upset, which acts presumably by diminishing the flow of blood through the liver. No connection appears between the phenomenon of the delayed curve (twice displayed among the faint cases) and the occurrence of fainting, since hepatic function is not impaired in cases showing delay.

Although it was not considered necessary to verify the retention of dye in patients with known hepatic disease, one such case (134) is

included at the end of Table VII for comparison with the fainters. The patient, a married woman aged 28, previously healthy, had developed jaundice with pyrexia, somnolence, vomiting, dyspnœa, swelling of the feet and abdomen, and slight enlargement of liver and spleen three months before the bromsulphalein test was performed. Her galactose tolerance had been found moderately impaired two months after the onset. At the time of the test she was much better, eating well and walking about the ward, but her skin was still bronzed (though the scleræ were no longer tinged), and she had lost 1½ stone during her stay in bed. Three months later she returned home free from symptoms, the liver and spleen being still palpable. Her indices (3·9 and 2·8) are much lower than those in the rest of the table.

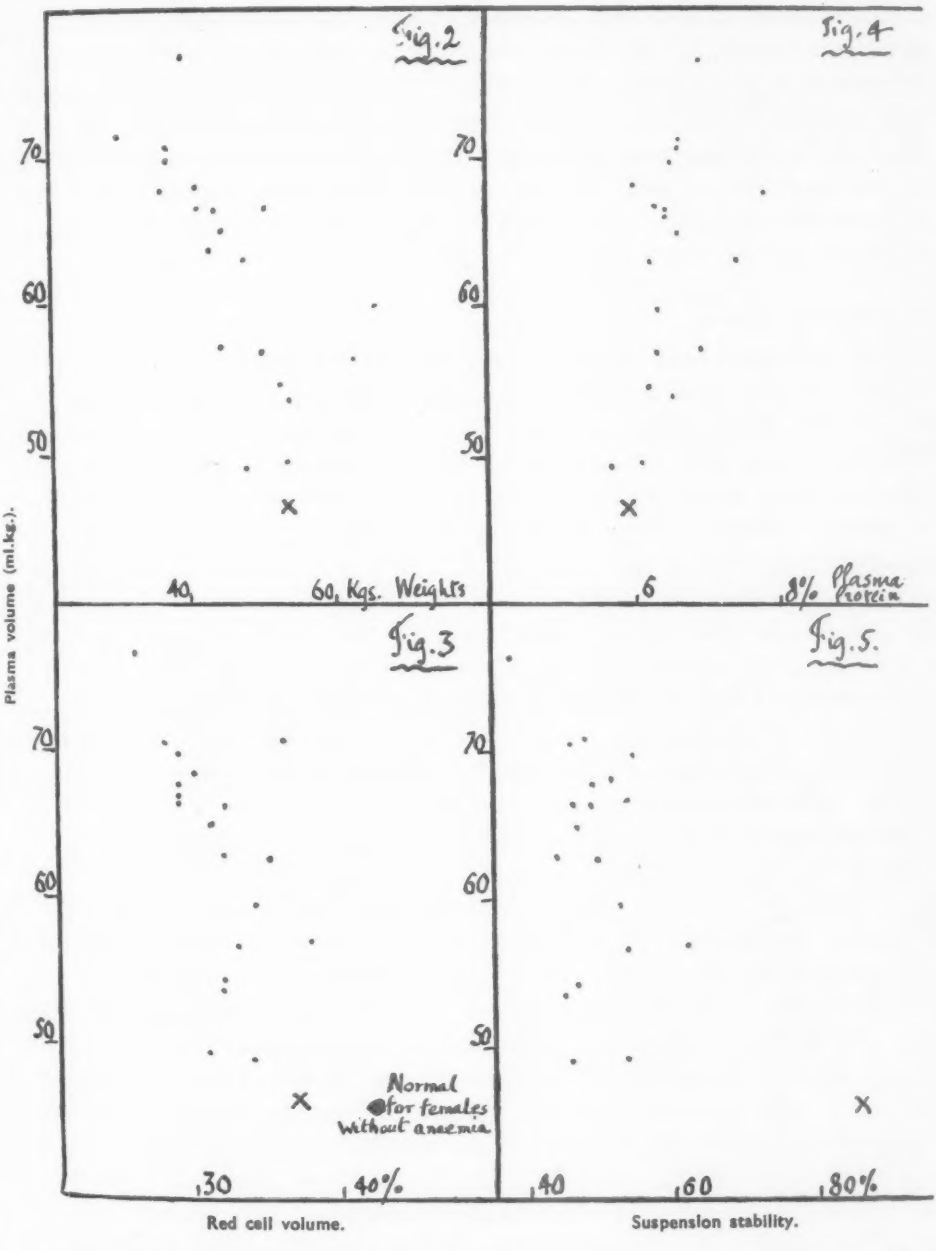
B. Plasma Volume.

Two obvious facts emerge from the data in Tables I, II and III: first, that the average plasma volume in female control cases is only 4 per cent. below that of the male controls, a considerably smaller difference than that between their red cell volumes; and second, that there is gross abnormality in the plasma volumes of the rheumatoid arthritics. Other chronic rheumatic diseases gave normal results, shown for subacute rheumatism in Table IV, for menopausal periarticular fibrositis in Table V, and for osteo-arthritis in Table VI. Rough assessment, by an earlier method, showed the plasma volume in gout to be normal, but in ankylosing spondylitis to be increased to about the same degree as in rheumatoid arthritis. The well known tendency for age and obesity to lower the ratio between blood volume and body weight was observed in the present series, as it was in blood volume determinations by the Congo red method upon osteo-arthritics (Sparks and Haden, 1932). Care was taken to ensure that gold treatments were not affecting results.

If now the plasma volumes (expressed as ml. per kg.) in Table II are plotted against patients' weights (Fig. 2), red cell volumes (Fig. 3), plasma protein percentages (Fig. 4) and suspension stabilities (Fig. 5) a definite tendency to linear relationship (in spite of ectopic points) appears in Fig. 2 (weights), a similar tendency appears in Fig. 3 (red cell volumes), though rather limited to the more anæmic cases, a less definite tendency appears in Fig. 4 (plasma proteins), while no relationship is shown in Fig. 5 (suspension stabilities). Moreover, the straight-line relationships suggested by the first three graphs are directed at or about the average values (marked by crosses) of the control cases, while the absence of linearity in the suspension stability graph is emphasised by the distance of the normal value from any conceivable line of relationship among the points.

Thus two inferences may be drawn: (*a*) that the increase in plasma volume observed is a true increase, since no other mechanism of over-

dilution of dye in the blood stream (such as concentration at a septic focus) would run parallel to body weight and red cell volume; and (*b*) that four abnormalities (of plasma volume, plasma protein, red cell



volume and body weight) occur in rheumatoid arthritis in association with each other, but distinct from the factor of suspension stability, forming a group of laboratory signs which might be called the "hydræmic syndrome."

The fact that this syndrome is independent of suspension stability (the only sign generally held to reflect the arthritis itself) indicates that it plays only an incidental, and not an essential part in the disease. A direct comparison between the intensity of the syndrome and that of the accompanying joint disease is difficult to make. Since it is impossible to measure the activity of a multiple arthritis, where various joints of various sizes are in various stages of disease, the term "flaring up" tends to be used indiscriminately of the joint and the general condition, principal criteria being (together with pyrexia) the factors of anæmia and wasting, which form part of the hydræmic syndrome itself. However, when attention was focused solely upon the activity of the joints in the present series (pyrexia, pain and synovitis only being studied) a definite absence of relationship to the hydræmic syndrome was observed. Case 84, for instance, was at the time of the test undergoing exceptionally severe activity in both hips; but she was plump, even healthy-looking, and her plasma volume is one of the lower values. Case 93 may be chosen as contrast to this picture, the suspension stability being practically the same and the anæmia rather less; here was a skeleton of a woman with enormously increased plasma volume whose joints crippled her so little that she was able to hop briskly around the building. Case 81 resembled Case 84 in having a nearly normal plasma volume, though her joint disease was less active; she was noted by the house physician as "of a healthy fat appearance with white skin," which again equates the degree of hydræmia with that of wasting, not that of arthritis. Indeed, the surest way of discovering clinically the probable presence of the hydræmic syndrome is by noting the degree of wasting of the interosseous muscles of the hands.

The normal plasma volume results obtained in menopausal periarticular fibrositis have a special suggestiveness. These patients are, as a rule, anything but wasted, there is no rise in plasma volume and seldom or slight in protein, though an isolated anæmia is usually present. The interesting possibility emerges that the absence of the hydræmic syndrome may be the actual factor of difference between this disease and rheumatoid arthritis; and consequently that the hydræmic syndrome in rheumatoid arthritis may be connected with an endocrine vector in the reverse direction to that of the menopause. In this connection it may be recalled that the thyroid gland in particular has been suspected of a part in rheumatism (Poynton and Schlesinger, 1931), and that points of similarity, rather striking in their diversity, exist between thyrotoxicosis and the "typical" acute rheumatoid arthritis of young women—namely, emaciation, nervous shock at onset, menstrual disorders, tachycardia, osteoporosis and diminished glucose tolerance.

C. Discussion of the Hydræmic Syndrome.

In order to make clear the magnitude of the abnormalities observed in rheumatoid arthritis, Table VIII, showing the reinforcement effect of the hydræmia upon the raised protein and its compensation effect upon the lowered red cell volume, has been compiled; total protein averages as much as 50 per cent. above, and total cells only 15 per cent. below, normal, thus reversing the usual order of importance assigned to these two factors in rheumatoid arthritis.

TABLE VIII

Case No.	*Plasma Protein in Grams per Kg. Body Weight.*	*Red Cell Volume in Ml. per Kg. Body Weight.*
80	4·54	28·6
81	3·01	22·1
81 (later)	3·58	28·0
82	3·38	25·7
83	4·09	29·2
83 later)	3·95	35·0
84	3·50	25·3
85	4·26	27·2
86	2·80	25·3
87	3·76	30·8
89	3·91	34·0
90	4·25	31·2
92	4·68	29·8
93	4·67	39·8
94	5·26	26·8
95	4·29	29·2
96	4·21	27·3
97	4·69	27·6
98	5·28	27·7
Average ..	4·11	29·0
Normal* ..	2·73	34·0

In the present work, where the rheumatoid arthritics were carefully selected severe cases, a rise in plasma protein percentage has been constantly and not sporadically recorded. Perhaps the inclusion of such cases as menopausal periarticular fibrositis in many rheumatoid investigations may have fostered the idea of inconsistency in this finding. The fact that the Kjeldahl results given here are lower than accepted normality was not further pursued, since their uniformity rendered them valid for comparative purposes.

To pin down the raised plasma protein of rheumatoid arthritics as either cause or effect of raised plasma volume calls for more evidence than is available here. It is more probable that a primary rise in protein (due to sepsis, presence of foreign protein, absorption of exudate) would draw up the plasma volume after it than the reverse, and

* Taking normal plasma protein as 5·8 per cent., cell volume as 42 per cent., and plasma volume as 47 ml./kg.

this view was taken in what appears to be the only previous record of a hydræmic syndrome—namely, a fatal case of rheumatic fever (Bradley, 1938) in which repeated readings of rising plasma volume and sedimentation rate paralleled falling red cell volume, hæmoglobin and red cell count; and the conclusion was drawn that the hydræmia, possibly due to increase of fibrinogen and globulin, was responsible for the major part of the anæmia and also for the increased sedimentation rate.

The present results do not support the idea that sedimentation is directly influenced by plasma volume (Fig. 5); but they do not conflict with the idea that anæmia may be. The simplest explanation of the direction of the linear relationship towards the normal value in plotting red cell volumes against plasma volumes (Fig. 3) is that of dilution of red cells by excess plasma. Moreover, the average total red cell volume of the rheumatoid cases of Table II, as calculated in Table VIII, is within 15 per cent. of normal—*i.e.*, about the same as that of the control cases of Table I.

The anæmia of all forms of chronic rheumatism has been described (Collins, 1935) as a hæmoglobin deficiency with a relatively insignificant fall in the red cell count, only 24 out of 75 female rheumatoid arthritics showing a red count below five million. These findings do not quite conform to those obtained here; for the average of the last hundred blood counts performed on female rheumatoid cases emerges as: hæmoglobin 74 per cent. (Haldane), colour index 0·84, red cells 4·4 million, and white cells (89 cases only) 7·7 thousand, the distribution of the colour indices being 0·663 for 8 cases below 60 per cent. hæmoglobin, 0·770 for 21 cases between 60 and 69 per cent. hæmoglobin, 0·829 for 35 cases between 70 and 79 per cent. hæmoglobin, 0·923 for 26 cases between 80 and 89 per cent. hæmoglobin, and 0·933 for 10 cases above 90 per cent. The cases were, of course, selected by the physicians from among the rheumatoid population of the hospital as those requiring blood counts; and a rather sluggish anæmia, intermediate between orthochromic and hypochromic, seems indicated.

The picture is similar to that of the anæmia of pregnancy, which has been described as an " oligocythæmia hypovolæmia " (Dieckmann and Wegner, 1934) with an increase in plasma volume (25 per cent.) and in total cell volume (20 per cent.). Total cell volume in the present series of rheumatoid arthritics, though not far from normal, was only twice raised above it (Table VIII). Further similarity exists in the raised fibrinogen level and lowered suspension stability of pregnancy.

D. Recapitulation.

The severe rheumatoid arthritis of young women may be divided into two syndromes—namely, (*a*) the essential impact of the disease

upon the joints, and (*b*) the hydræmic syndrome, in which the degree of loss of flesh, rise in plasma volume, rise in plasma protein and oligocythæmia run parallel to each other. It is further suggested that a considerable part of the anæmia is a mere dilution effect, though not on that account any the less effective as an anæmia; and that the hydræmia may be caused by the rise in blood protein which is so marked a feature of the disease. This rise in protein, together with the emaciation, is to be derived from the unknown "poison" of rheumatoid arthritis only via endocrine imbalance, whereas the effect of the poison upon the joints is direct, thus accounting for the observed independence of the hydræmic syndrome and the joint disease.

VI. Summary

1. A spectrophotometric acetone extraction method is described for the determination of bromsulphalein in blood.

2. By this method, liver function has been found within normal limits in chronic rheumatic disease.

3. By the same method, plasma volumes of chronic rheumatics have been determined, with the disclosure of gross abnormality in rheumatoid arthritis.

4. Changes in plasma volume, plasma protein, body weight and red cell volume in rheumatoid arthritis have been found to vary roughly in proportion to one another.

5. These four factors are described as the "hydræmic syndrome," whose relation to the essential joint condition is discussed.

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A CLINICAL CONTRIBUTION TO THE STUDY OF THE ÆTIOLOGY OF THE FIBROSITIC NODULE

By W. S. C. COPEMAN

The term " nodule " is employed in the title of this paper, as it is one that has become familiarised by custom. It has seemed, however, that the existence of a nodule sufficiently definite to be palpated in the muscles of a sufferer with fibrositis must in most cases be a sign of chronicity of the complaint, and that the " myalgic spot " is probably an earlier stage of what later becomes a nodule if left untreated. The discrepancy in the frequency with which nodules are found in this disease in England and in America can be explained by this hypothesis.

The myalgic spot is an area of hyperæsthesia in the substance of a muscle or its tendinous sheath which gives rise to pain either in the same locality or referred to a distance when stimulated. We owe mostly to Kellgren the description of this referred pain and its distribution. These spots are generally multiple and occur in the powerful muscles of the back and of the gluteal region; often towards the edge of the muscle, where it blends with the more fibrinous portion. They may also occur, but less frequently, in the peripheral muscles, and in the anterior muscles of the trunk.

The ætiology and pathology of the myalgic spot or nodule is unknown, although trauma is believed by most observers to play a part in its development. It is thought that the observations recorded in this paper throw some light on the ætiology in a proportion of cases.

Observations on Acute Myalgia

An epidemic of influenza was recently studied in which severe pain in the lower back was an early and prominent symptom in nearly every case. Some patients also complained later of pains in the thighs, calves, and arms.

The cases comprising this epidemic were all of the " febrile" type described by Horder and Gow (Price's " Medicine," 1941) as being of abrupt onset, with pyrexia and associated malaise and headache in addition to the pains described above. The pyrexia was high for three to five days and accompanied by a moderate degree of catarrh chiefly affecting the eyes. Defervescence was by rapid lysis, and a leucopenia was present in most cases. None of the forty patients examined had any previous history of rheumatism.

It was noted in the course of this epidemic that although the acute lumbar pain was diffuse, severe, and resulted in spasm in some cases, by careful examination it could be found that it radiated from localised

hypersensitive areas in the adjacent muscles; and that the position of these areas approximated to those usual in cases of ordinary lumbago. The same observation was made in cases where the pain was in the limbs.

In one instance also severe " crampy " pain in the upper portion of the rectus abdominis muscle was met with—the clinical picture being comparable with Bornhölm disease. This pain was entirely relieved by an injection of procain at the focal point.

The subjective pain disappeared after two or three days, but these myalgic spots were found by palpation to be still present, although the patient was not aware of their presence. When they were found and pressed on he experienced a sudden sharp pain which made him wince momentarily and which was—in about half the cases examined—referred in addition to the whole area previously affected.

The number of such spots which could be found in any patient tended progressively to decrease as time went in.

The same group of patients were again examined two months after their influenza, when it was found that only in rather less than half of them could these spots still be found. In these cases, as before, the patient was himself unaware of their presence until examination.

Three cases deserve special mention.

Case 1 *: A Civilian aged* 40.—Sudden onset of headache with pain behind the eyes, sweating and malaise. Pain in the back had occurred several hours previously, and this got progressively worse. The patient preferred walking about rather than lying in bed for this reason, although his temperature was 102·6.

On examination the patient looked ill and was sweating profusely. The eyes were congested and the tongue furred. Pain in the back was evidently severe and the muscles appeared to be in spasm.

Urine and stools, normal. Blood, no malarial parasites W.B.C. 5,000.

Next day the patient was much better. There was still pain behind the eyes and in the back. The temperature was normal. Myalgic spots were found in the lumbar region. The patient made an uninterrupted recovery, but three weeks later he developed mumps. The pain then returned to the lumbar region as at first, although not so severely, for two days during which the temperature was raised above 100° F.

Case 2 *: A Civilian aged* 27.—Complaining of sudden onset of severe pains in head, back, and legs, with feeling of pyrexia, previous afternoon. Temperature was 101·6, pulse 90. When seen, he was sweating profusely. No shivering; bowels rather loose on previous day but now constipated. Patient looked ill tongue lightly furred. On examination: abdomen—nothing abnormal found; blood—no malarial parasites, W.B.C. 3,400. The pains had prevented much sleep previously, but sedatives gave some relief.

One week later pain and other symptoms had entirely gone, and patient had resumed work. Pain could, however, be provoked momentarily by pressure on the myalgic spots which still persisted in lumbar region and along the border of the ilium on both sides. Two weeks later the condition was unchanged, excepting that fewer of these spots could be found. Those present were carefully marked.

Five c.c. of blood, taken in the first 12 hours, from a patient who had just developed sandfly fever, was then injected intramuscularly—by permission—

and on the next day a pyrexial attack with a maximum temperature of 101° developed and lasted 36 hours. The patient complained of lumbago from the onset of this pyrexia, and on examination it was found that this pain was originating from the spots which had been marked. It was easily abolished by injecting 1 per cent. novocaine into them.

One month later this patient was still found to have three myalgic spots in the lumbar region of which he was completely unaware.

Case 3 *: A Gunner aged* 22.—Sudden onset of severe occipital headache with pains in back and legs. Temperature 101°.

On examination patient looked and felt very ill. Marked congestion of the conjunctivæ; the bowels had been rather loose for two days. Tongue moist with light brown fur. Abdomen—normal. Stools and urine—normal. W.B.C. 4,200.

Pains disappeared on third day; temperature normal and all symptoms gone on fifth day.

Two weeks later patient stated when seen that he was perfectly well, but well-defined myalgic spots were found in lumbar region. On pressure these referred a pain down the legs entirely comparable with that which had occurred during onset of fever.

This patient was seen again a month later for another reason, and volunteered the information that similar pains had returned, although in a lesser degree, for a short period a few days previously whilst he was starting a cold in the head.

From these observations it seems that infection with the organisms of influenza will produce acute muscular pain which can be shown to be referred from myalgic spots which develop in the region of the affected muscles. The spots appear to be comparable with those found in cases of ordinary lumbago. A large proportion of the spots which were seen to develop in the present series of cases disappeared a few days after the termination of the influenza. A proportion, however, survived.

It does not seem that these myalgic spots are a specific reaction to the virus of influenza as such, however, in view of the fact that the pain returned temporarily in the same areas during an attack of mumps which one of the patients (Case 1) developed spontaneously during convalescence.

This view was confirmed experimentally by inducing an attack of sandfly fever artificially in a patient convalescent from influenza (Case 2), with the same result.

It also seems possible (Case 3) that periodical attacks of the common cold or other mild virus infection may prove to be a factor in keeping active myalgic spots which have arisen in this way, although confirmatory evidence is lacking. If this were found to be so it suggests an analogy with the " maintenance dose " in other fields.

Observations on Myalgia following Exanthemata

It is well known that acute muscular pains may arise in the course of, or after, many of the acute infectious diseases other than influenza; chiefly it would seem those of virus origin. A considerable number of patients complaining of pain that had arisen in this way have been examined during the past year. These pains have also in the majority of cases been found to have their origin in well defined hypersensitive myalgic spots from which the patient's myalgia or " neuritis " (muscular tenderness) was referred. The diseases which most commonly give rise to this syndrome appear to be sandfly, glandular, undulant and scarlet fevers, measles and rubella.

Myalgic spots arising during the course of one of these diseases have

been found to be still present two months later; this being the longest period during which " follow up " proved possible in this series.

The description already given of the myalgic spots arising during the epidemic of influenza applies equally to those arising in this series and justifies the belief that they may arise during the course of almost any acute infectious fever, and that a certain proportion will persist unknown to the patient until such time as they may subsequently become reactivated.

It seems probable that such factors as chill, damp, trauma and mild focal infection, which have sometimes been held to be causative, are in fact of secondary importance, and will only provoke an attack of fibrositis or myalgia in the presence of latent myalgic spots formed previously in this way. The method whereby they actually provoke an attack may possibly be by inducing a local œdema in the sensitive area whereby the victim becomes aware of the myalgic spot and of the pain referred from it. If this is so it accounts for the nodular feeling which is not infrequently remarked at these points, and the fact that this can sometimes be rubbed away by a skilful masseur.

Summary

1. The rôle of " myalgic spots " or " rheumatic nodules " in fibrositis is discussed.

2. In a recent epidemic of influenza in which lumbar and other pain was a prominent feature, it was observed that this pain was also referred from small hypersensitive areas in the muscles. These were indistinguishable from " rheumatic " myalgic spots.

On re-examination of the patients after one and two months these spots were still found to be present, although in diminishing numbers. The patient was, however, invariably unaware of this fact until pressure from the examining finger disclosed them. None of these patients had any previous rheumatic history.

3. Myalgic spots which had arisen during influenza were reactivated in one patient by an attack of mumps which arose spontaneously during convalescence. In another case this occurred as the result of the artificial induction of an attack of sandfly fever by the inoculation of infected blood.

It appears therefore that myalgic spots can arise *de novo* in the course of acute influenza, and that these will in a proportion of cases persist. They can, however, be reactivated by infections of other types. There was evidence in one case suggesting that the common cold provided the means of maintaining the activity of the myalgic spots.

4. Rheumatic pains are a characteristic sequel of many of the exanthemata, mostly those of virus origin. Observation has shown

that these pains, which tend to arise in a less acute manner, are also generally of the focal type.

5. The final suggestion is therefore that the myalgic spots which it is now widely agreed form the basis of many of the rheumatic syndromes of later life are sometimes a legacy from acute infections in earlier life. It is important to remember that the victims are often unaware of their presence until they become activated by factors such as chill, trauma, or focal sepsis. These factors should therefore be regarded as secondary and no longer causative in such cases.

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NEW PATHS OF INVESTIGATION FOR DIAGNOSIS AND THERAPY

By Dr. ERNST FREUND

Since 1828, when Woehler discovered a method of producing urea in the test tube, thereby proving that some of the substances of organic life could be produced *in vitro*, pathological investigation has progressed towards a more precise understanding of the activity of the human organism in the sphere of biochemistry.

The study of chemical phenomena, aiming at qualitative and quantitative determinations of the waste products of metabolism, was thus encouraged with a view to the possibility of distinguishing between pathological and normal metabolism, and of this becoming the basis of diagnosis and therapy. There can be no doubt that such a development offers considerably better prospects of effective therapy than the empirical employment of substances of the mineral, plant and animal worlds, dating from the earliest age of medicine (admittedly with very beneficial results in some aspects of the art of healing).

Progress in development must necessarily be sectional. A complete survey of the vast range of biochemical problems involved in the utilisation of varied substances by the human organism, and the waste products of the process of utilisation, is a task of such magnitude that it can be only usefully approached little by little. This paper will deal with certain aspects of diagnosis and therapy arising from a comparison of the effects on the cells of material in the urine coming respectively from (*a*) healthy and (*b*) morbid subjects.

We can easily ascertain how much of the ingested food is employed

in the body; how much is used up in producing heat and activity. We can note whether this is occurring in a normal manner, or whether anomalies attributable to deficiency in the organs are occurring. Indeed, in a number of cases we are able to determine, by means of "load tests," the capacity of some organs. But the question, "Is a serious illness present?" which is so important both to the doctor and the patient, is only rarely answered by evident deficiency in an organ. But the promising field is being opened up of biochemical investigation of the "waste products" eliminated by the various organs.

Let us picture the conditions prevailing in an organism or in the cell of an organism. Its chemical constituents, its store of substances, are subject to continuous change; and change can be intensified or reduced by the action of heat and cold, or by the ingested food, or even by the breathing—that is to say, by external reagents. Also, apart from these reactions, the cell of the organism is subject to influences which from youth to a certain age may be constructive, and at a later age may be destructive. There can be no doubt that the constructive and destructive processes may proceed side by side in the cell. But so far research has concentrated chiefly on katabolism. Under the impression that katabolism is incomparably greater than the anabolism that must be ascribed to the tissues, investigators have studied chiefly the former, regarding the latter as secondary, because it could only be governed from the cell, which takes from the sea of nutrient juices flowing to it the substance which the miracle of selectivity enables it to take.

Now what happens when the organism is ill? In some cases the organs lose weight, become emaciated, so that parts of the cells must have been destroyed. In other cases the cell is diverted from its right functions of maintenance and of normal growth and there follows the creation of superfluous or malignant tissue. What effects this morbid process and in what circumstances? The answer is—apart from the natural degenerative conditions of "wearing out" by age—external enemies, either of a physical character, as heat and cold, or micro-organisms.

Consider the physical conditions first. The initial effect of heat or cold on a particular group of cells coming into contact with them does not finish the matter. That effect may spread to other cells not directly involved. This compels the assumption that destructive ferments have been set in motion (and this can be demonstrated on living tissue by means of autolytic experiments). Where do these ferments come from?

We know that the most important digestive ferment of the intestinal canal, trypsin, becomes inactivated on entering the serum, and that it may be partially reactivated through slight acidification. On the

basis of this example it is possible to postulate that each cell contains constructive and destructive ferments, which can be inactivated when linked with each other or with other substances, and can be activated by certain stimuli. Thus the effect of an external attack on a cell will depend on which of the ferments is liberated, and which, when already liberated, can be inactivated again, or eliminated from the cell and the organs. To throw light upon these questions it is of particular value to examine the urine for constructive or destructive ferments, and to see whether there is any difference in the action of those ferments on added tissue extracts in a state of health and illness respectively. The investigation was to be not of digestive ferments, but ferments for cell components. It was therefore of importance to discover, in the first place, whether ferments destructive of the nucleus of the cell were present (nucleases). For this purpose in a series of experiments I prepared alkaline extracts of an organ, precipitated out the nucleoproteids with acetic acid, and used the nucleoproteid solution which remained in the form of a cloudy solution after the acetic acid had been washed out as a reagent. I used 0·05 g. per cent. N of this nucleoproteid, adding 1 to 10 c.c. urine, then alkalising to approximately pH 8·5, so that phenolphthalein did not turn pink, adding one drop of chloroform, and leaving the mixture to stand at a temperature of 37°.

After ten hours it could be noted that healthy urine destroyed this nucleoproteid to such an extent that no turbidity, or only traces, could be obtained with acetic acid. But the urine of a person with a sick organ had not only lost its power of solvency for the nucleoproteid of that organ, but had often acquired an anabolic power for it.

As a complement to this finding, investigation of extracts from healthy and morbid organs showed that in the case of healthy organs added peptone exerted a constructive action, while in the case of morbid organs it exerted a destructive action. Thus we have the following conclusion: in the healthy organs constructive ferments for the cell-extract substance are at work; in the morbid organ destructive ferments; and as the examination of the urine shows, the healthy organ sends destructive ferments into the urine, while the morbid organ is incapable of this and, as far as can be ascertained, sends constructive ferments into the urine.

These facts have been completely confirmed in urine examinations repeated a thousand times (see also confirmations by Bume, *Wr. klin. Woch.*, 1936, 46, and Lustig, *Klin. Woch.*, 1937, 2). The differentiation goes so far that it is possible to distinguish between a disease of the small and large intestine. The corresponding ferment actions of the serum are accordingly of a contrary kind to those of the urine. This opens up the possibility of supplementing the knowledge we are able to acquire through auscultation and percussion with the study of the chemical functions of the individual organs regarding their cell material. The

reaction on the nucleoproteids naturally represents only the beginning of this study, which must be extended to all the other great groups of cell substances as fats, carbohydrates, lipoids, etc., and to the extent of this constructive or destructive process, so that the kind of organ destruction may be determined and also whether the products involved are, functionally, cardinal or secondary products.

Thus, to complement the diagnosis (*e.g.*, in the case of hypertrophies), the urine result may be compared with the construction or destruction of the serum, and the quantitativity of the reaction may be investigated.

However, from the point of view of diagnosis it will not be sufficient to know that an organ is diseased; it will also be necessary to determine the kind of disease. We must know whether it is tuberculosis, or a purulent disease, or degeneration, etc.

There is a possibility that the sick organ will show a stronger inhibition to katabolism than the normal organ. To investigate this it would be necessary to proceed in the following manner:

Take the case of a rheumatic joint. We can prove that the joint is morbid, but we do not know whether the morbidity is rheumatic in origin or otherwise. It will be necessary to submit to digestion another organ, say muscle, which in the healthy state is normal for the urine concerned, in order to discover whether constructive or destructive action takes place. In some cases it will perhaps be necessary to mix a healthy organ with the toxin concerned and thereby poison it. In this way it would be possible—and past experiments have shown this possibility—to diagnose the kind of illness as well.

However, as to the question whether a grave illness is present, it is not necessary to make tests for all organic illnesses; it is sufficient, as investigations have shown, to test the nucleoproteid of the serum—as a sort of representative of the entire organism—with the urine.

However, diagnosis is not the ultimate aim, only an aid to the ultimate aim of therapy. But this study also offers a new possibility for therapy.

It is a medical view dating back to antiquity that the organ that is sick should be fed with the same organ substance. The modern method of injections of extracts aims at this therapeutic action. But the urine reaction in question—that is, the testing of the functions of the organs as regards construction and destruction—affords a further possibility of extract of precisely the right substance. If the healthy organism sends the destructive ferments into the urine and retains the constructive ferments, then, by preparing extracts from the organ, it must be possible to determine the substance which acts particularly constructively—that is, the one which, when added to the urine, impedes the destructive process.

This determination can be carried out by adding to the normal

urine, which acts destructively, the organ extracts, and determining the one that impedes the destructive action. This organ extract, after being isolated and concentrated, would have to be tested for its therapeutic action. Possible therapeutic action in this respect would possess the advantage over other therapeutic measures with injections of organ extracts. Up till now the functional products, so to speak, have been injected, so that only a replacement of the original product is effected, whereas the injection of constructive substances would not only normalise the organ, but also increase its normal productivity. This effect could be proved by means of perfusion experiments.

Steyskal in Vienna has already reported on a number of therapeutic effects in kidney cases which he obtained with organ ether extracts which I have supplied.

All these suggestions are merely an indication of a path that has yet to be explored. But when it is explored, the physician may be able to do for the sick organism what the healthy living cell does for itself through its most essential property—recruitment of its substance.

In the investigation of rheumatic diseases we have carried on at the Pearson Foundation some experimental work on lines indicated in this paper. This work was much hampered by lack of sufficient clinical material which would enable tests to be carried out under control conditions.

The fact that if people are exposed to what are accepted to be factors promotive of rheumatic disease (such as damp and cold) all do not develop rheumatic symptoms points to the assumption that these are due not only to such external stimuli, but also to predisposition or metabolic anomalies.

In search of such anomalies, we investigated whether rheumatic urine behaved differently from non-rheumatic urine in the presence of joint extracts. We found that, whereas normal urine digests added nucleoproteid of normal joints at 37° C. to such a degree that no clouding can be obtained with acetic acid, rheumatic urine left added nucleoproteid completely unchanged.

The diagnostic application of this reaction proved itself to the extent that an improvement of the rheumatic condition was indicated by the fact that the patients' urine had recovered its power to digest nucleoproteid from joints. True, this only proved a morbid state in the joint, not necessarily a rheumatic state.

War conditions prevented us from obtaining rheumatic joints for such diagnostic investigation. Therefore we tried to produce "rheumatic substances," so to speak, by poisoning normal joint extracts with extract substances from rheumatic fæces. It had been ascertained from earlier investigations that if, at the onset of the disease, rheumatic fæces were inoculated into superfatted milk, a bacterium-free extract could be obtained from the milk, which, if

injected into mice, caused swellings of the joints of the hind legs. This reaction was evidently due to special substances in the food, for the same process with peptone solution produced no such effect. Extracts of this " rheumatised " milk were applied to joints or joint extracts, and thus there was obtained from the joints nucleoproteids which, while digested by normal urines, remained undigested by rheumatic urines. This indicated a possibility of the diagnosis of the rheumatic state.

Further investigations showed that the " toxic " substance is a fatty acid which can be isolated as a calcium salt and which, if injected into the neck of mice, causes difficulty of movement in the joints of the hind legs.

As regards therapy, these results suggest the conclusion that abnormal acids exerting a harmful action on the membranes of the joints are produced in the intestinal canal through abnormal fermentative processes and point to a therapeutic method of treating rheumatism by means of intestinal disinfection, with simultaneous alkalisation.

EMPIRE RHEUMATISM COUNCIL

SEVENTH ANNUAL REPORT

NOVEMBER, 1942, TO NOVEMBER, 1943

MY LORDS, LADIES AND GENTLEMEN,

THE hope that this, the seventh completed year of our work, would allow members to assemble in Annual Meeting has been again deferred by war conditions, but we may have reasonable confidence of meeting in 1944. Meantime this report records the progress of the past year.

With deep regret I have to note the death of two of our Vice-Presidents, Lord Hirst of Witton and Sir Benjamin Cohen, both generous supporters of the Council; of Sir Francis Fremantle, M.P., and Dr. Geoffrey Holmes and Dr. F. J. Poynton, two of our keen scientific workers.

The Right Hon. Tom Williams, M.P., Parliamentary Secretary to the Minister of Agriculture, has accepted office as a Vice-President of the Council, a welcome addition to our ranks. He is strongly interested in the War on Rheumatism, and this link with Agriculture will be valuable since wholesome diet is an important factor in dealing with rheumatic disease.

Treatment

The terms of the agreement arrived at last year between the Empire Rheumatism Council and the British Orthopædic Association for co-operation in securing the most effective and economical national treatment for rheumatic sufferers have been placed before the Minister of Health. His reply was cordially sympathetic and contained the assurance that the Ministry "will not lose sight of the important bearing which Rheumatism has on the organisation of the Health Services." We hope shortly to have direct discussion with the Minister regarding the assurance given in October, 1941, of the intention of the Government in its Public Health policy "to ensure that everyone will receive the treatment appropriate to their needs."

The national advantage to be gained by ending the past neglect of the adult rheumatic sufferer can be effectively illustrated by the statistical evidence of progress in regard to the one form of Rheumatic Disease which has been vigorously combated during the past few years. In "Rheumatism—A Plan for National Action" there was recorded the reduction, between 1926 and 1937, from 2 to 0·77 per cent. of the incidence of heart disease in the children coming under the London School Medical Service. With caution in dealing with vital statistics covering only a short period of years, it was suggested that this might be, at least in part, due to the excellent work of the London County Council Schools Rheumatism Scheme. Corroborative evidence to support that suggestion has come from the vital statistics for England and Wales during the five years period 1938-42. Deaths from Acute Rheumatism (which may be accepted as largely synonymous with Juvenile Rheumatism) fell steadily from 1,104 in 1938 to 503 in 1942. Further evidence comes from our Research Foundation dealing with the incidence of Acute Rheumatism among a large body of youths, which reports a steep decline during recent years.

It is contrary to the principles of medical science to claim too much; to fall into the mistake of interpreting *post hoc* always and to the full extent as *propter hoc*. But there is at least some probability of a close relation between the two facts: that for Juvenile Rheumatism and its *sequelæ* there has been, since 1926, a great and increasing measure of effective treatment *and* a steady decrease in the incidence of *sequelæ*; whereas, for Adult Rheumatism, means of effective treatment have been available for only a small percentage of sufferers and there is no evidence of any decrease.

Reports from Treatment Centres, with which we are in correspondence, record great increases in the number of patients seeking treatment; difficulties in maintaining the Medical Staffs to meet this pressure owing to the call on practitioners for the Defence Services; and success of treatment in a very high average of cases where the rheu-

matic condition had not been too long neglected. At the West London Hospital Rheumatism Department the number of patients treated almost doubled in 1943 as compared with 1942.

Our correspondence with individual sufferers has been considerable; only rarely can we recommend to the patient an efficient Treatment Centre convenient to his, or her, residence to which the family doctor can refer the case.

Laboratory Research

During the year Temp. Surgeon-Commander C. A. Green, Director of our Naval Research Foundation, has—following the direction given to him in 1939 by our Council—continued to carry out confidential pathological work for the Admiralty Medical Services apart from his Rheumatism Research work. This has called for much extra work on his part (cheerfully undertaken); an increase in the number of laboratory assistants and in laboratory accommodation (cost met out of Naval funds). Recent growth in the demands on him for work apart from Rheumatism search has led to negotiations, initiated by the Admiralty but yet awaiting final confirmation, which will lead to a future considerable saving of the Council's funds and yet provide for the Rheumatism Research work to be continued.

That work during the past year has been extensive, covering flocculation tests of an anti-body in certain rheumatic sera and anti-histase titration and anti-histase serum treatment (these three carried on in collaboration with Dr. E. W. Todd, the Serum Institute, Carshalton): virus work; and preliminary work in the study of penicillin.

Valuable results have come from this Foundation since its inception in 1938; some of which may prove to be pointers for further progress.

Professor Freund and his assistants, at the Hammersmith laboratories of the Frederick Pearson Foundation, carried on, until the middle of the year, a research as to the relations of abnormal intestinal digestion with rheumatic disease.

Dr. Dyson has continued his virus research using the equipment of the Sir Alexander Maclean laboratory.

Clinical Research

During the year tasks of clinical research into the value and correct dosage of gold salts in the treatment of some forms of rheumatic disease; into the efficacy of an enzyme preparation; and into other suggestions regarding treatment have been continued. No definite conclusions can yet be announced. I call attention again to the great difficulty in carrying to conclusive results clinical investigations owing to the lack of Centres at which tests can be carried on under

adequate control conditions among considerable groups of patients for a sufficiently long term. We may hope that the promised post-war development of the National Health Services will remedy this lack.

On this aspect of our work grateful acknowledgment is given to the many correspondents, medical and lay, who have taken the trouble to write to our Council communicating observations they have made from their experience, either as doctors or as patients. Before the war this correspondence came from all quarters of the globe—proof of the scope of our publicity work; lately it has been more restricted but still considerable. A few suggestions are merely faddist; a great number are redundant because they record well-known facts; there is a residuum giving possibly useful hints. These suggestions have been communicated to clinical workers or carefully recorded for future test.

Overseas Activities

It was my privilege on behalf of the Council to assist an educational campaign in the U.S.A. against Rheumatic Fever instituted by the Metropolitan Life Assurance Company in conjunction with the Public Health Services. A full report on prevention and treatment in Great Britain was furnished. In preparing that I was greatly assisted by Dr. Thornton of the London County Council Medical Services. It is a good feature of the United States social structure that the Life Assurance Companies devote considerable sums to medical research and medical education—a policy which is beneficial to the community and also to their own particular interests. In our country, as you know, the Prudential Assurance Company, chiefly through its Approved Society Section, have followed this admirable example in supporting the War on Rheumatism.

A cabled report from Moscow records an interesting discovery by Academician Alexander Bogolometz of a serum which is claimed to have definite effects in the treatment of arthritic conditions arising from Rheumatic Disease. I have communicated with this Russian scientist asking for further particulars and inquiring whether it is possible to send a supply of the serum for testing in this country.

Our honorary medical Secretary, Lt.-Col. Copeman, whilst on duty in Malta, enlisted the interest of the Chief Medical Officer and of other prominent practitioners there in the War on Rheumatism. The institution of a local branch of the Empire Rheumatism Council has been sanctioned; further particulars of its constitution will be available shortly and will come before you for final approval.

Australia continues to take a keen interest in our work; new developments are being promptly communicated to the Health Authorities there. We may hope that, so soon as peace returns, Australia will revive the proposal to hold a Continental Medical Congress to establish a Rheumatism Council affiliated with our own.

The Official Journal

Our Official Journal has maintained its high standard despite difficulties arising from war conditions in this country and the United States and affecting both the Editorial Board and contributors. Members are urged to extend the circulation of the Journal; new subscribers can obtain at discount rates on application to our office a full set of back numbers, representing a comprehensive survey of research work in the Rheumatic Diseases during the past six years.

Administration

Attention is being given to the problems which our Council will face in the post-war period; as to how best we may shape our activities within the framework of the reorganisation of the National Health Services. So soon as the new policy has been definitely determined there will be submitted to members for their consideration a plan for the future.

I wish to express my sincere thanks, and that of my colleagues on the War Emergency Committee, for the generous confidence which members have shown to us during the past four years. There has not been any objection or criticism expressed during all that time though—to use a political analogy—the Cabinet has not been able to meet its Parliament. Members in their turn will wish to express their great appreciation of the devoted work of the War Emergency Committee, viz., Dr. C. W. Buckley, Dr. Hugh Burt, Lt.-Col. W. S. C. Copeman, A. G. Timbrell Fisher, Dr. Mervyn H. Gordon, Col. the Rt. Hon. John Gretton, Brigadier F. D. Howitt, Sir Walter S. Kinnear, T. W. Robinson and H. Gordon Thompson. With their help my task as Chairman has been singularly care-free, though much important work has been done under conditions of difficulty imposed by the war. To the Staff our gratitude is also due for faithful service.

Generous help has been accorded to our work by the Press, both lay and Medical, during the year. In spite of the heavy demands on their space, the chief journals have given good attention to all important developments in the War on Rheumatism.

The foundation of the British Association of Physical Medicine (of which I have accepted the Presidency for its inaugural year) brings a valuable ally to the campaign against rheumatic disease. Our friendly alliances with this and the British Orthopædic Association constitute a good "United Front."

I look forward with confidence to meeting members in 1944 and to hearing from them that they are content with the effort maintained during the years of war and that they are fully resolved to carry on the campaign vigorously, in no wise discouraged by the measure of delay which war has imposed, but rather prompted to more intensive

effort. As in "that other war," Time is an important factor; urgent is the need to put a limit to the perennial ravages of Rheumatic Disease.

(*Signed*) HORDER.

BOOK REVIEW

ARTHRITIS AND ALLIED CONDITIONS. By Bernard I. Comroe, M.D. Henry Kimpton. Pp. 878.

The appearance of two editions of a book of this size in less than twelve months confirms the favourable views that were expressed when it was first published. It also indicates that increasing interest is being taken by the profession in this hitherto neglected group of diseases.

Comroe's "Arthritis" cleverly combines detail and outline. In the main it is a book of reference, but interspersed throughout are numerous summaries in box form in which the salient features of theory, pathology and treatment are clearly set out. By reading these summaries and nothing else the practitioner can gain a comprehensive view of the rheumatic diseases.

There are fifty chapters, of which the first twenty-two are on the subject of rheumatoid arthritis, which is dealt with from every conceivable aspect. Separate chapters follow on the other forms of arthritis and also rheumatic fever. There is a lengthy chapter on the foot, a chapter of eighty-six pages on backache, and a much shorter chapter on sciatica. The book ends with a chapter on the sulphonamides, which was not present in the first edition and is an excellent summary of present knowledge.

Much of the book has been rewritten, the chapter on chrysotherapy almost entirely so. The Americans are still chary about giving gold, and still require the patient to sign an affidavit to say that he is willing to take the risks involved. There is, however, a shift towards the gold standard, and Sabin and other American workers are devoting a great deal of work to finding a less toxic compound.

Some of the chapters are very good indeed, particularly those on the general treatment and the question of diet in rheumatoid arthritis.

The author is clearly more at home when writing about arthritis than he is when dealing with non-articular forms of rheumatism. The chapter on fibrositis in particular is unconvincing, and it is not at all clear whether Comroe believes the American view that fibrositis should not, or the British view that it should, be considered as a disease. Prolapsed intervertebral disc is discussed under backache and not in the chapter on sciatica, and there are other similar inconsistencies.

In a book of this size one would have liked to see a more detailed description of the rarer conditions, such as Boeck's sarcoidosis (with X-rays) and dermatomyositis, which at first may easily be mistaken for rheumatoid arthritis. The chapter dealing with "diseases mistaken for rheumatoid arthritis" mentions these conditions, but in not a great enough detail.

The book is beautifully got up, profusely illustrated, and contains a large number of references. It is certainly to be regarded as an outstanding book on the Rheumatic Diseases.

H. A. B.

ANNALS
OF THE
RHEUMATIC DISEASES

THE OFFICIAL JOURNAL OF
THE EMPIRE RHEUMATISM COUNCIL

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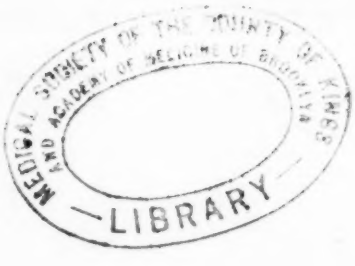

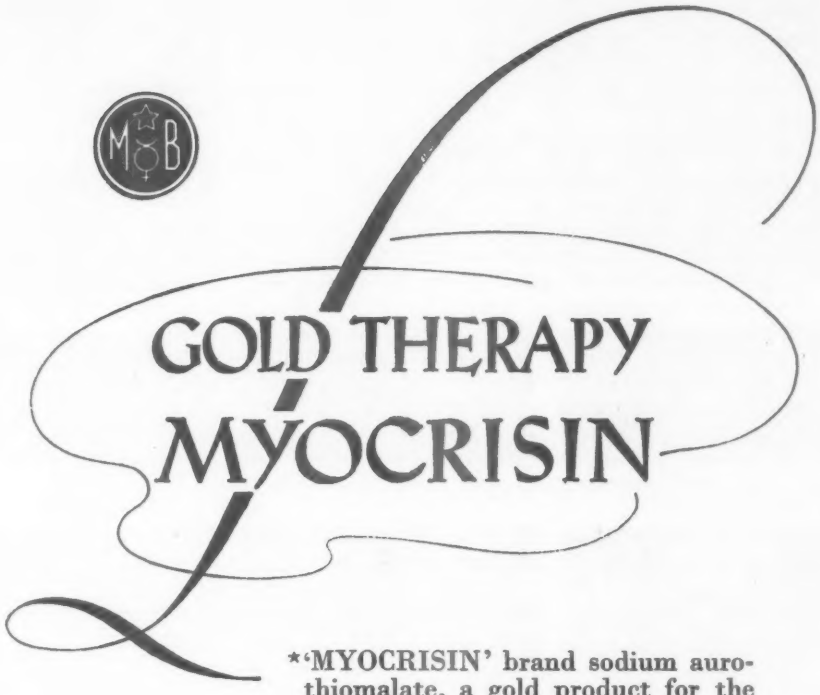

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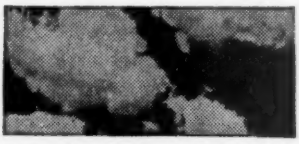
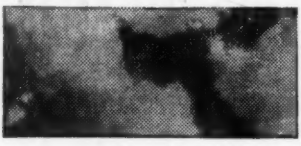


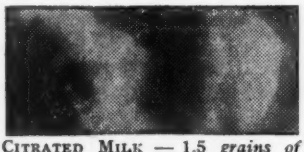
BOILED MILK—*The milk was momentarily brought to boiling point.*



DILUTED MILK—1 *part milk and* 1 *part water.*

LACTIC ACID MILK (Special) — *Lactic Acid B.P. added drop by drop until milk just begins to curdle*

LACTIC ACID MILK — 30 *drops of lactic acid B.P. added per pint of milk.*



CITRATED MILK — 1.5 *grains of sodium citrate added to* 1 *fl. oz. of raw milk.*

CITRATED MILK (Boiled)–1.5 *grains of sodium citrate added to* 1 *fl. oz. of raw milk and the mixture brought to the boil*

DILUTED MILK — 1 *part milk and* 2 *parts water.*

MILK AND BARLEY WATER — 1 *part milk to* 1 *part Barley Water.*

MILK AND CREAM — 1 *part milk to* 1 *part cream.*

BENGER'S FOOD *prepared by standard formula and self-digested for* 5 *mins.*

BENGER'S FOOD *prepared by standard formula and self-digested for* 15 *mins.*

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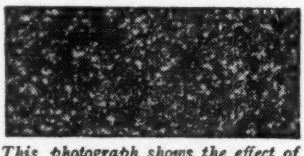
An infant's gastric juice contains the enzyme rennin rather than pepsin.



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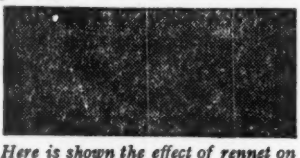

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